REMARKS

The claims are 26-33 and 36-37, with claims 26-30 being independent. Claims 34 and 35 have been cancelled without prejudice or disclaimer. Claim 27 has been amended to correct a formal matter. Claims 28 and 29 have been amended to include the recited figures.

The Examiner objected to the specification as failing to provide a description of the drawings. The specification has been amended to include a brief description of the drawings.

Claim Rejections – 35 U.S.C. §112

Claims 26-37 were rejected under 35 U.S.C. §112, first paragraph, allegedly as failing to comply with the written description requirement. Claims 28 and 30 were rejected under 35 U.S.C. §112, second paragraph, as allegedly incomplete. Applicants respectfully traverse each of the Section 112 rejections that have been made in this case.

Rejection of Claims 28 and 30, Re: Incorporation of Figures

Claims 28 and 30 were rejected under 35 U.S.C. §112, second paragraph, as allegedly incomplete because the claims are not self-contained. Applicants note that claims 28 and 29 refer to Figures. As argued previously, claims 28 and 29 were written to refer to a figure in the specification in accordance with M.P.E.P. 2173.05(s). Claims that are written to incorporate by reference a specific figure or table are not improper and are not considered indefinite. Applicants respectfully submit that M.P.E.P. 2173.05(s) provides full support for drafting claims to incorporate by reference to a specific figure or table, where "there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim." These claims present a situation where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. However, to expedite prosecution of this case, claims 28 and 29 have been amended to include the recited figures. It can be noted that each of these claims, which used to be 4 lines long, now take up a full page. It is clearly more concise to incorporate the figures by reference into claims 28 and 29 than duplicating the drawings into these claims.

Applicants hereby approve any Examiner's Amendment that will cancel the added figures from claims 28 and 29.

Rejection of Claims 26-37, Re: Lack of Description

The Examiner has alleged that there are a number of deficiencies in the subject specification. To summarize, the Examiner contends that there is an alleged lack of description as to:

1. whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form or solvates claimed (page 2);
2. the claimed pharmaceutical compositions in terms of their X-ray powder diffraction pattern or infrared spectrum data (page 3);
3. whether or not the hydrate is actually maintained in the composition and in the tablet or capsule (page 3);
4. whether or not the compound in the composition actually treats diabetes mellitus and any unknown condition associated with diabetes mellitus (page 3);
5. whether or not the polymorph and not the original compound treats diabetes and all the conditions associated with diabetes (page 3);
6. how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed (page 3);
7. how the polymorph forms and compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment of diabetes mellitus and all unknown conditions and complications whatever they may be (page 3);
8. all of the alleged products (page 4);
9. whether the instant compound, composition, tablets or capsules containing the instant compound treats diabetes, all conditions and complications associated with diabetes (page 5);
10. whether the instant polymorphs treat diabetes and moreover, all the unknown conditions associated with diabetes (page 5);
11. any unexpected or unobvious properties of the claimed polymorph vis-à-vis the original compound (page 6);
12. the pharmaceutical compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed (page 6);

13. whether the instant polymorph rather than the original compound treats diabetes and any of the unknown conditions and complications thereof (page 6).

Objection Nos. 4, 5, 9, 10 and 13, Re: Treatment of diabetes mellitus

Solely to expedite prosecution, Applicants have cancelled claim 35 which encompassed treatment of conditions associated with diabetes mellitus and complications thereof. Applicants respectfully submit that the subject specification does provide sufficient guidance as to the conditions and complications of diabetes that may be treatable by administration of the compound of this invention. The Examiner's attention is directed to page 3, lines 12-24, where examples of "conditions associated with diabetes mellitus" and "complication of conditions associated with diabetes mellitus" are provided. Applicants specifically reserve the right to prosecute claims directed to the use of the claimed 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate for the treatment of conditions associated with diabetes mellitus and complications thereof in a subsequent continuation/divisional application.

The Examiner contends that the subject specification allegedly fails to demonstrate whether the claimed compound treats diabetes. The Examiner also contends that the subject specification allegedly fails to demonstrate whether the claimed compound, rather than the original compound, treats diabetes. Applicants respectfully request clarification as to which compound the Examiner is referring to by the term "original compound."

Applicants respectfully submit that the anti-diabetic activity of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione was well established prior to the filing date of the subject application. See U.S. Patent No. 5,002,953 (corresponding to EP 0306228), U.S. Patent No. 5,741,803 (corresponding to WO94/05659), U.S. Patent Nos. 5,708,012, and Cantello (newly cited). Applicants respectfully submit that based on the established anti-diabetic activity for 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, one skilled in the art would anticipate that other pharmaceutically acceptable salts, hydrates, and hydrates of salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, or a tautomer thereof, would also demonstrate anti-diabetic activity. (See CN 1277965, already of record in this case). Moreover, both 35 U.S.C. §156(f) and the Food, Drug & Cosmetic Act define the term "drug product" to include the active ingredient (which in the present case is 5-[4-[2-(N-

methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, or a tautomer thereof) as well as any salt or ester of the active ingredient.

> Human drug product means the active ingredient of a new drug or human biologic product (as those terms are used in the [FD&C] Act and the Public Health Service Act), including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

Food, Drug & Cosmetic Act, 21 C.F.R. §60.3(b)(10)

Accordingly, Applicants respectfully submit that the art recognition of the anti-diabetic activity of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, together with the statutory recognition that various derivatives of an active ingredient will demonstrate the same biological activity as the active ingredient, obviate any need for an actual clinical showing that the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of the present invention may be used to treat diabetes. Withdrawal of Objection Nos. 4, 5, 9, 10 and 13 is respectfully requested.

Objection Nos. 1, 3, 6-7 and 12, Re: Compositions and Maintenance of Crystalline Form

It should be noted that the Examiner's rejection of claims 26-37, on the grounds that the specification allegedly failed to provide description as to whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form claimed and how the pharmaceutical composition can be prepared in order to maintain the particular compound form, included the rejection of compound claims 26-30, process claims 31-32 and method of treatment claim 36. Applicants respectfully submit that none of claims 26-30, 31-32 and 36 recite "pharmaceutical carrier" as an element of the claim. Applicants have discovered a novel crystalline hydrated form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione hydrochloride, that is suitably stable for characterization by IR spectroscopy and XRPD pattern analysis. Accordingly, Applicants respectfully request withdrawal of the Section 112 rejection and allowance of claims 26-30, 31-32 and 36.

The pharmaceutical composition claims 33 and 37 are directed to those compositions that contain the claimed form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, where such form, when analyzed by IR or XRPD, provides the claimed IR or XRPD data. Applicants

wish to note that the subject claimed compound is not a true polymorph, but rather a pseudopolymorph:

> Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. In addition, solids may form solvates and hydrates, also called pseudopolymorphs.

Chemical and Engineering News, February 23, 2005, page 32.

The Examiner has cited a number of references in an effort to provide some basis to support the Section 112, first paragraph, rejections in this case. However, Applicants respectfully submit that the references relied upon by the Examiner do not provide such support, and in some instances actually contradict the conclusions that the Examiner attempts to draw from the references. For example, the Examiner relies on the disclosure of Brittain, page 290 to support the statement that desolvation of a polymorph may occur, presumably during formulation of the claimed compound or when the claimed compound is contained in a pharmaceutical composition. The disclosure at page 290 of Brittain relates to the determination of metastable solubilites. Brittain discloses that during dissolution of a metastable polymorph, conversion to a more stable polymorphic phase may occur and that such conversion may occur by one or more of at least six different processes. One of the processes listed is desolvation. The discussion at page 290 of Brittain does not relate to pharmaceutical compositions, 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, pharmaceutical compositions containing 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate or dissolution studies of any of the above. Moreover, the Examiner has failed to provide any scientific theory that relates metastable solubilites, or the determination thereof, to the claimed pharmaceutical compositions.

The Examiner also states that processing of a compound into a pharmaceutical composition could create a different polymorph than the polymorph being claimed or even back into the compound itself. The Examiner refers to pages 912-913 of Haleblian.

Applicants respectfully request clarification as to which compound the Examiner is referring to by the phrase "back into the compound itself."

The disclosure at pages 912-913 of Haleblian relates to various problems that might occur during the preparation of suspensions (aqueous vehicles or creams), solutions and suppositories. Haleblian discloses that, while in suspension, a polymorph might convert to a more stable polymorph which might result in an uneven distribution of the drug in the suspension. Haleblian also discloses problems with suppositories that involve polymorphism of the suppository base, not the drug product. There is no discussion of any problems that will occur during the preparation of a pharmaceutical composition containing the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of this invention. The Examiner has provided no explanation as to how these theoretically potential problems, none of which seem to be more or less relevant to 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate, will render one skilled in the art incapable of making or using a pharmaceutical composition of this invention.

The Examiner further relies on the disclosure of the Chemical and Engineering News article for the assertion that formulation of drugs or pharmaceuticals in metastable forms is "highly unpredictable." Applicants respectfully submit that the C&EN article actually discloses that the search for polymorphs is highly unpredictable:

> "But no method yet exists to predict the polymorphs of a solid compound with significant certainty. The search for polymorphs is largely an empirical process."

Chemical and Engineering News, February 23, 2005, page 32.

Regarding formulation of drugs, the C&EN article states (at page 33) that "some polymorphs are more difficult to formulate than others because of their shape or hygroscopicity." The C&EN article also states "And 'what's really important during storage is not to have a conversion from one form to another. Otherwise, your tablet will either turn into powder or into concrete. It won't have the same bioavailability any more[.]'"

Applicants respectfully submit that these statements, without more, fail to support the Examiner's position in this case. The disclosure of the C&EN article merely identifies properties of polymorphic materials that should be monitored or assessed during formulation development. Moreover, it can be noted that most of the formulation issues identified are not particularly unique to polymorphic or pseudopolymorphic compounds. The formulation of

any new drug substance must address the physico-chemical properties of that drug substance, i.e., shape of the drug substance (crystallinity or lack thereof and crystal/solid form - needles, plates, etc.), hygroscopicity, chemical stability (stability of the compound itself, e.g., during storage - heat/humidity stability) and stability of formulations (e.g., assessment of interactions between the drug substance and excipients in the formulation). The only formulation issue that is unique to polymorphic compounds is the theoretical possibility of conversion to another form. As will be discussed below, Applicants respectfully submit that those of ordinary skill in the art, using routine experimental techniques, know how to test and evaluate such conversion issues – if and when they appear.

The Examiner contends that "metastable forms will disappear" (page 5) and change into the most thermodynamically stable form. At page 7 of the Office action, the Examiner asserts alternatively that "polymorphs tend to convert from less stable to more stable forms" (line 8) and that "[p]olymorphs can convert from one form to another" (line14). However, the Examiner also asserts that "it is well known that polymorphs can convert to the original compound." (page 8). Applicants respectfully submit that the mix of such statements makes it difficult to discern the Examiner's position on polymorph behavior and more particularly, on pseudo-polymorph behavior. Clarification is respectfully requested. Clarification of the term "original compound" is also specifically requested.

Applicants respectfully submit that the correct assessment of polymorph/pseudo-polymorph conversion is that it might occur – which includes the situation that such conversion does not occur. For example, it is well recognized that metastable forms can be stable indefinitely– without converting to a more stable form. Some polymorphs may only convert to more stable forms under conditions that the polymorph will not be exposed to under routine handing/processing conditions. (See newly cited Concise Encyclopedia Chemistry, 1994, pg 873 and C&EN, page 32: "The rate of conversion depends on the required activation energy and the differences in free energies [between forms]").

The C&EN article relied on by the Examiner actually contradicts the statement that "metastable forms will disappear and change into the most thermodynamically stable form." The C&EN article provides examples of situations where more stable polymorphs of drug products had been discovered, but where the less stable form of the drug was the form that was selected for development into a pharmaceutical product. In the exemplified situations at Abbott and Bristol-Myers Squibb, processes to prepare the less stable form and stable

pharmaceutical compositions containing that less stable form were developed. Clearly, metastable polymorphic forms of some drug products can be stable, can be stable in the presence of more stable forms, can be prepared from more stable forms and can be processed into commercially stable formulations.

Applicants respectfully submit that there is no deficiency in the subject specification. Those skilled in the art know and understand that crystal form conversion may occur or may never occur. This is the state of the art and it is clear from the art of record, particularly the C&EN article and the newly cited Phadanis and Chakravarty references discussed below, that those skilled in the art know and understand how to develop crystalline compounds into commercial drug products. The Examiner has cited no art nor presented any argument that indicates that one of ordinary skill in the art, applying routine experimentation, would not be able to make or use a pharmaceutical composition containing the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of this invention.

Applicants respectfully submit that the subject Section 112 rejections are based on theory, not fact – on the theoretical possibility that crystal form conversion might occur. There is simply no factual basis or support in any of the cited art for the assumptions inherent to these rejections - that the claimed compound crystal form is inherently unstable or unstable in the solid state, that some action needs to be taken to maintain and/or prevent the claimed form from converting into other forms or that the presence of specific pharmaceutical carriers is required to maintain the claimed form. The Examiner has cited references that disclose problems that might occur or that have occurred during handling of other specific compounds. However, there is no indication, no suggestion, no prediction that any of these problems will occur with the crystalline hydrochloride dihydrate of this invention. Withdrawal of Objection Nos. 1, 3, 6-7 and 12 is respectfully requested.

Objection No. 8, Re: All Products

The Examiner is also objecting to the specification as allegedly failing to place all of the alleged products in the possession of the public without inviting more than routine experimentation.

Applicants respectfully submit that the subject specification discloses 3 methods for preparing the hydrochloride dihydrate of this invention. The specification also provides 2

spectroscopic means of identifying the crystalline form of the hydrochloride dihydrate. The Examiner has failed to provide any reason as to why one skilled in the art would not be able to use these methods to prepare and identify the crystalline hydrochloride dihydrate of this invention.

Regarding the claimed pharmaceutical compositions, the Examiner has failed to provide any reasons as to why one skilled in the formulary arts, applying routine experimentation, would not be able to prepare pharmaceutically acceptable compositions containing the hydrochloride dihydrate of this invention. Cited in the IDS filed herewith are articles by Phadnis et al. (1997) and Chakravarty (2005). Phadnis et al. (1997) describes the preparation and evaluation of a series of pharmaceutical compositions containing different drug substances, some of which are different hydrate forms or different polymorphic forms. It can be noted that no polymorph or hydrate conversion was observed in any of the pharmaceutical compositions prepared and studied by Phadnis or Chakravarty. These references indicate that those skilled in the art can perform drug substance identification by analysis of characterizing data (i.e., XRPD patterns or DCS (differential scanning calorimetry) profiles). These references also exemplify some of the analysis techniques that may be used to analyze and compare the characterizing data to known data (e.g. pattern subtraction analysis).

The potential of inoperative embodiments (e.g., compositions containing an excipient that may be incompatible with the claimed compound) does not render the composition claims of this invention inoperative. The standard is whether a skilled person could determine which embodiments would be operative or inoperative with no more effort than is normally required in the art. As stated above, because most of the formulation issues identified by the Examiner are not unique to the formulation of polymorphic or pseudo-polymorphic compounds, Applicants respectfully submit that those of ordinary skill in the art, using routine experimental techniques, will know how to evaluate such issues without undue experimentation. Moreover, as evidenced by the articles by Phadnis or Chakravarty, skilled persons, using routine spectral/XRPD pattern techniques, can assess the chemical/structural integrity of drug substances in formulations. Withdrawal of the Examiner's objection is respectfully requested.

Objection No. 11, Re: Unexpected Properties

The Examiner further contends that the specification allegedly fails to show any unexpected or unobvious properties of the claimed compound over the original compound. Again, identification of the "original compound" is respectfully requested.

Applicants note that this objection was made under 35 U.S.C. §112, first paragraph. A showing of unexpected or unobvious properties is not an element of the written description requirement. Accordingly, Applicants respectfully request withdrawal of this objection under 35 U.S.C. §112, first paragraph.

Objection No. 2, Re: XRPD Patterns of Compositions

The Examiner has objected to the specification for allegedly failing to provide the X-ray powder diffraction pattern or infrared spectrum data for the claimed pharmaceutical compositions.

As Applicants described previously, many conventional pharmaceutical carriers/excipients are crystalline materials and most pharmaceutical compositions are mixtures of more than one carrier/excipient. Accordingly, the Examiner appears to be requesting/requiring XRPD pattern data for a mixture of one or more unspecified carrier materials, selected from the hundreds of FDA-approved pharmaceutical excipients, some of which may be crystalline, with the crystalline 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of this invention. The Examiner has provided no scientific or legal basis for considering the subject specification to be deficient for not providing XRPD patterns for such unspecified mixtures of materials.

Applicants direct the Examiner's attention to Phadnis et al. (1997) and Chakravarty (2005), cited in the IDS filed herewith. Phadnis et al. (1997) describes a series of pharmaceutical compositions prepared using different active ingredients, some of which are different hydrate forms or different polymorphic forms. These references indicate that those skilled in the art can identify the drug compounds in compositions using, for example, XRPD pattern analysis. These references also indicate that different excipients (particularly crystalline vs. non-crystalline excipients) demonstrate different behaviors when subjected to XRPD analysis, sometimes requiring pattern subtraction to remove the contribution of an excipient to the XRPD pattern. Such analysis may be performed by comparing the XRPD

patterns of the pharmaceutical compositions to *the XRPD patterns of the individual drug compounds*. Notably, the constant element in these particular analyses is the XRPD patterns of the individual drug compounds.

Applicants have provided an XRPD pattern for the hydrochloride dihydrate of this invention in Figure 2. Applicants have also provided on page 1, lines 28-29 specific diffraction pattern peaks that may be used to identify the subject hydrochloride dihydrate. Accordingly, Applicants respectfully submit that XRPD data provided in the subject specification is sufficient to enable one skilled in the art to identify the hydrochloride dihydrate of this invention.

Although Phadnis and Chakravarty used XRPD (and DSC) to assess drug substance identity, it will be understood by those skilled in the art that depending on the components of the pharmaceutical compositions (e.g., identity, characteristics and concentration of the carrier(s) and drug substance in the composition), other techniques such as Raman, IR and/or solid state ^{13}C NMR may be more useful in such assessments. Applicants respectfully submit that use of each of these techniques for compound and crystal form identification is routine in the art.

Applicants respectfully request withdrawal of this objection under 35 U.S.C. §112, first paragraph.

Rejection of Claims 28 and 30, Re: "Substantially"

Claims 28-30 were rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. The Examiner contends that the term "substantially in accordance" in claims 28-30 is allegedly indefinite.

Applicants note that claims 28 and 29, which refer to Figures, contain the phrase "substantially in accordance." Accordingly, Applicants response will relate to claims 28 and 29, not claims 28-30.

Applicants respectfully submit that the term "substantially" or "substantially in accordance" as used in the pending claims is not indefinite. It is well established that the term "substantially" is not indefinite when it serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention and to distinguish the claimed subject matter from the prior art (See Verve, LLC vs. Crane Cams, Inc., 311 F.3D 111, 1120, 65 USPQ 2d (BNA) 1051, 1054 (Fed. Cir. 2002). The use of the term

"substantially" or "substantially in accordance" in the pending claims relates to either an IR spectrum or an X-ray powder diffraction (XRPD) pattern, whose exact appearance is dependent upon a variety of experimental parameters – factors that are recognized and understood by those skilled in the art (as well as the courts, see *In re Grose,* 592 F.2d 1161, 201 USPQ 57 (CCPA 1979)). For example, it is well recognized that the precise peak location and/or intensity in an IR spectrum or an XRPD pattern (or the corresponding spectrum/pattern data) obtained for a given compound can, and often will, vary slightly from one spectrum/pattern to another due to such factors as differences in the concentration of the compound in the analysis sample, the temperature at which the data was collected, the manner of preparation of the specific compound sample (degree of grinding, manner of packing, presence or absence of other materials in the sample, etc.), and/or the identity of the instrument used to obtain the spectrum or pattern. Because such considerations are routinely present when comparing experimental data to literature data, Applicants respectfully submit that those skilled in the art will know and understand how to interpret such IR and XRPD data to determine whether the compound that provided such experimental data is the same as the compound that provided the IR and/or XRPD data as claimed, or whether it is different.

Applicants respectfully submit that those skilled in the art will know and understand that a spectrum or pattern does not need to be identical to that of a reference spectrum or pattern to positively identify the compound that provided that spectrum or pattern as identical to or different from the reference compound. Similarly, Applicants respectfully submit that those skilled in the art will know and understand that an IR spectrum or XRPD pattern does not need to be identical to that provided herein to positively identify the compound that provided that spectrum or pattern as identical to or different from the claimed hydrochloride dihydrate crystalline form of this invention. The Phadnis et al. (1997) and Chakravarty (2005) references exemplify the identification of different drug compounds in pharmaceutical compositions. It can be noted that in the XRPD pattern analysis described in these papers, differences (e.g., the absence of certain peaks or changes in peak intensity) between experimental pattern data and reference pattern data were analyzed and attributed to sampling conditions (effects of sample dilution, preferred orientation of crystals in the sample holder) or to instrumentation limitations (lack of resolution of the diffractometer). In each case, the authors did not consider such differences to be a barrier to the identification of the drug

substance. Applicants respectfully request withdrawal of this objection under 35 U.S.C. §112, first paragraph.

Other:

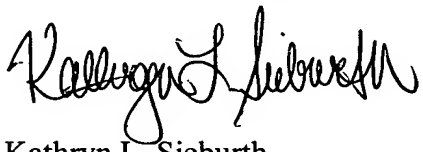
Applicants wish to clarify that neither the clinically effective dosage nor a commercial pharmaceutical dosage form for the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride dihydrate of this invention has been determined. In the previous Response, Applicants stated that "a useful formulation and dosage form for a pharmaceutical composition of this invention is a tablet containing 1mg - 12mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione." That statement should have read "a useful formulation and dosage form for a pharmaceutical composition of this invention may be a tablet containing 1mg - 12mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione." A clinically useful formulation and dosage form for the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione maleate disclosed in U.S. Patent No. 5,741,803 (corresponding to WO94/05659) is a tablet containing that amount of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione maleate equivalent to 2, 4 or 8 mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione. (U.S. Patent Application Publication No. 20020177612). It is anticipated that a similar formulation and dosage would be suitable for the compound of the present invention, but it has not been confirmed that an identical formulation and dosage is clinically and commercially suitable. Applicants maintain, however, the determination of clinically effective dosages and the preparation of commercial pharmaceutical dosage forms for the hydrochloride dihydrate of this invention, based on the established dosage and forms for 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione maleate, can be performed by those of ordinary skill in the art without undue experimentation.

Applicants believe that they have addressed each of the Examiner's concerns and met each of the objections. If the Examiner has any remaining objections or concerns, the Examiner is respectfully requested to contact Applicants' undersigned attorney to resolve such issues and advance the case to issue. If the Examiner maintains any of the above Section 112 rejections in the next Office Action, Applicants respectfully request the Examiner to

specifically respond to the rebuttal arguments presented in this Response so that Applicants can better understand and address the Examiner's objections or concerns in this case.

This Amendment is being filed together with an Information Disclosure Statement and a Petition for Extension of Time. In the event that these papers get separated, or there is any deficiency in the Petition, this constitutes a Petition for Extension of Time for the minimum period required to effect timely filing and consideration of this Amendment and Information Disclosure Statement, together with authorization to charge any fees under 37 C.F.R. §1.16 or §1.17 which may be required by these papers to Deposit Account No. 19-2570.

Respectfully submitted,



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